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Translation of "Struktura i funkstiya vestibulyarnogo apparata v usloviyakh izmenennogo gravitatsionnogo polya"

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STRUCTURE AND FUNCTION OF THE VESTIBULAR APPARATUS UNDER CONDITIONS OF AN ALTERED GRAVITATIONAL FIELD

Ya. A. Vinnikov

Manned space flights, which were first accomplished by the Soviet Union, have required that special attention be given to the role of the vestibular apparatus and to possible changes in its functional state during conditions of weightlessness.

In doing so, the obstacle of an insufficiency of knowledge concerning the structure and function of the vestibular apparatus, particularly the part responsible for perception of the position of the body relative to the gravitational field (the utricle in vertebrates) was encountered. In this connection, besides theoretical problems, it seemed necessary to take account of the practical requirements of astronautics, in particular methods of preventing vestibular and vestibular-sympathetic disturbances caused by the effect of acceleration and weightlessness on the vestibular apparatus.

Currently it may be considered as demonstrated that the receptors of the utricle are stimulated by changes in the body's position in the gravitational field, as well as during exposure to radial accelerations (Prosser and Brown, 1961). In this may be discerned the ultimate function of the utricle, which is connected with the continuous statotonic reflexes in the muscles of the extremities, trunk, and neck, and with the symmetrical and asymmetrical vestibular reflexes. However, the details of the mechanism of the utricular function, the nature of stimulation of the utricular receptor cells by the forces (or energy?) of gravity, and also the processes of excitation and transmission in the form of impulses, which according to the current view are formed in the sense organs on the cellular, subcellular, and molecular levels of organization—these questions are so far practically unexplained. At the same time it is perfectly clear that only knowledge of the mechanism of action of the "organ of gravity" on the cellular and subcellular levels can serve as basis for purposefully affecting its function.

Electron microscope and histochemical investigations conducted in our laboratory show that the "organ of gravity" in the representative vertebrates studied (fishes, amphibians, reptiles, birds, and mammals) present a number of distinct cellular and subcellular evolutionary forms, reflecting not only the extent of their general organization, but also variations in the ecological position of the animals in the gravitational field. For example, in fishes, which live in the water and therefore are under special conditions of interaction with the gravity field, the utricle contains only cylindrical receptor cells (type 2), crowned with a bundle of stereocilia supporting an enormous otolith, and with a single oriented moveable kinocilium. Cells of the second type are distinguished by several buttom-shaped nerve endings at their basal extremity (those light in color being afferent, and the darker ones, filled with synaptic vesicles, being efferent), which are clad in myelin almost all the way to the synaptic membrane (Figure 1). The utricles of fish are strongly reminiscent of their lateral line organs (Flock and Wersäll, 1962).

Turning to dryland vertebrates, in reptiles (Ya. A. Vinnikov and L. K. Titova, 1962) and in mammals (Wersäll, 1961; Engström, 1960), besides the cylindrical ciliated cells there appears a new modification of ciliated receptor cells, the jug-shaped ciliated cells of type 1, which according to our data attain their greatest degree of development in the birds, which follow an aerial mode of existence (Figure 1).

Type 1 cells are also crowned with a bundle of stereocilia supporting an otolithic membrane with small otoliths or otoconia, and with a single moveable kinocilium uniformly oriented on every cell. But unlike type 2 cells, the type 1 cells are set in individual cup-shaped nerve endings, so that the whole external plasmatic membrane of the cell except for the ciliated tip becomes a synaptic surface with an enormous area. The external surface of the nerve cup as a rule is the site of "dark" nerve endings, apparently representing axon-axon synapses, which at the present time are assigned an inhibitory function (Gray, 1961).

Although in guinea pigs and mice one such nerve cup will contain one type 1 cell, in mice and monkeys, as a rule, it will contain two, and in birds it may contain up to five or seven. In the latter case each of the cells nested in the common cup will have its own inclination and spatial orientation different from that of the neighboring cell (Figure 1). The phenomenon of several type 1 cells sharing one and the same cup is accompanied by a sharp increase in complexity of the nature of their synaptic contacts with the nerve endings. This fact perhaps may be explained from the point of view of Khartlayn's (1962) induction theory related to photoreceptors.

In birds changing their position relative to the vector of the earth's gravity in flight, only those ciliated receptors can be stimulated whose position is thereby changed. On the other hand, the remaining ciliated cells located in the same synaptic cup must be in a state of inhibition. Consequently, the excited state of the ciliated cells must be intensified against the background of their inhibited

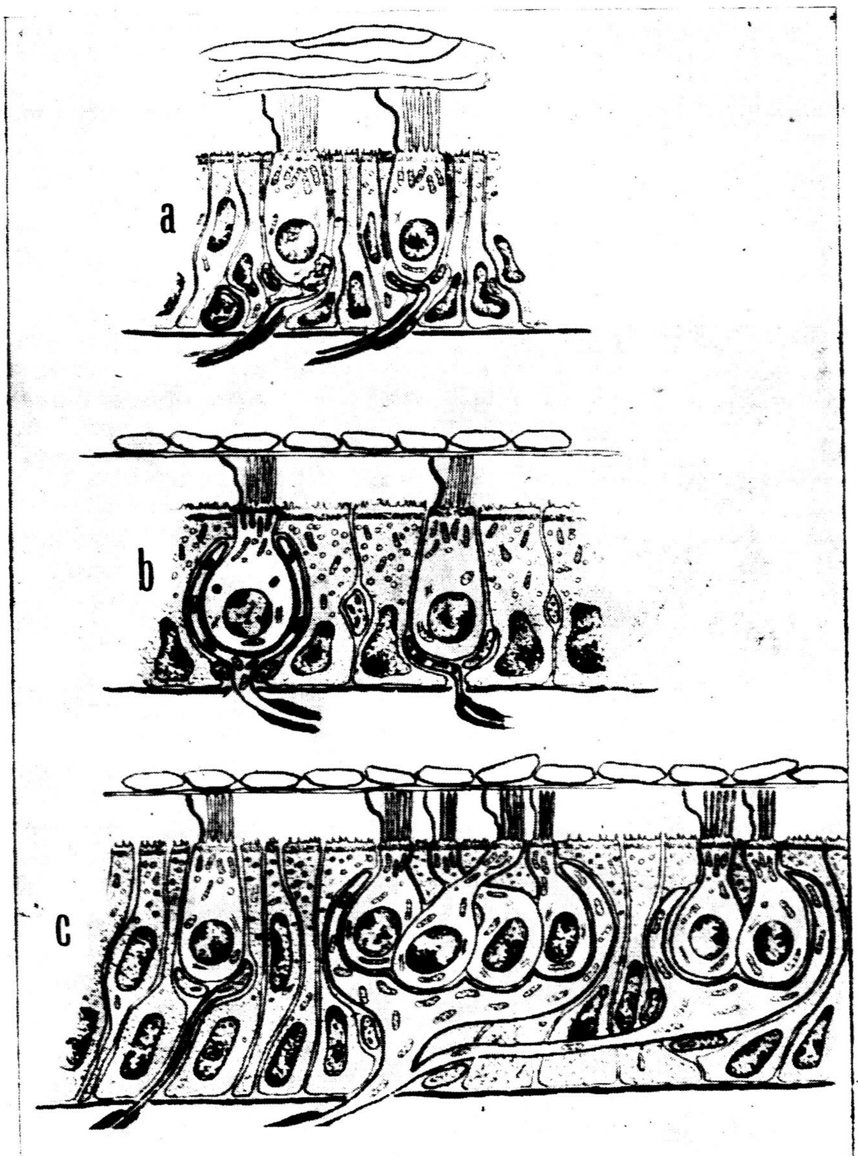

Figure 1. Diagram of the cellular and subcellular organization of the "organ of gravity"—the utricle.

a—fishes; b—mammals; c—birds.

neighbors. But could it not be altogether a matter of devising a reliability principle of the functional system of the utricle? This exposition apparently reflects the utricular function in birds not only as the "organ of gravity", but also as a navigational instrument (Screiber, Qualtierotti, and Mainardi, 1962).

Thus, the cellular and subcellular organization of the ciliated cells and the nature of their synaptic connection in the utricle of vertebrates displays a number of variants of gradually increasing complexity, which may be explained by the progressive changes in position of animals in the gravitational field during their (evolutionary) emergence from the water onto dry land, and then into an aerial environmental medium. In other words, to a greater or lesser degree, they have the capability of actively altering their position in the gravitational field.

However, along with the above, a constant differentiation of the apical part of the receptor cells of both type 1 and type 2 is observed in all vertebrates, which consists of a uniform structure of the bundles of stereocilia and the single kinocilium, containing 9 pairs of peripheral and two central fibrils, uniformly positioned on each cell. This establishes the unchanging nature of stimulation and the unanimous significance of stimulus perception in the utricle of vertebrates which is not dependent on the environmental medium, despite the simultaneous drastic evolutionary transformation of the part of the cell where the excitation is transmitted to the appropriate synapse. Consequently, the mechanism of stimulation of the "organ of gravity" does not change in the course of the evolution of vertebrate animals.

The difficulty of understanding this stimulation is connected with the paucity of our information about the physical nature of gravitation. Nonetheless, comparison of the substructural organization of the lateral line organs of fish with the utricle, which in the lower vertebrates ontogenetically and phylogenetically constitutes a single acoustico-lateral system, reveals a number of analogies which make it possible to assume some similarities between the stimulatory processes of this system, at least, and the moveable kinocilium. By using the electron microscope it has been shown that in the receptor cells of the lateral line organs, the position of one kinocilium will also be oriented (in a certain way) with respect to the stereocilia bundles of the two adjacent elements (Trujillo-Cenoz, 1961; Flock and Wersäll, 1962).

But unlike the utricle and the crests of the semicircular canals of the labyrinth, in which according to our data and the data of Löwenstein and Wersäll (1962), the position of the kinocilium in all receptor cells is always the same, its position in the lateral line organs in two adjacent receptor cells will be reversed with respect to the remaining bundle of stereocilia. In one of the adjacent cells the kinocilium will be oriented toward the anterior end of the canal, and in the other, toward the posterior end.

In the opinion of Flock and Wersäll (1962), this opposed orientation of kinocilia in the lateral line organ along the long axis of the body is connected with the fact that the liquid in the canal can move either toward the tail or toward the head, and the kinocilia are thus enabled to sense the direction of movement of the liquid in either case. In contrast to this, in the pecten of the ampullae of the semicircular canals the kinocilia are always oriented in one direction, that of the current set up in the endolympha by angular accelerations. Actually, the kinocilia are oriented toward the utricle in the horizontal canal, and in the opposite direction in the vertical canal (Lowenstein and Wersäll, 1959). It has been shown that adequate stimulation--movement of the endolympha in the semicircular canal in the direction of the stereocilia--is accompanied by a lowering of the microphone effect and an increase in activity currents, while movement of endolympha in the direction of the kinocilia is accompanied by inhibition (Trinker, 1957, 1959; Flock and Wersäll, 1962; Löwenstein, Osborn and Wersäll, 1964). Therefore it is correct to assume that under conditions of adequate stimulation sharp shifts of the otolithic membrane or the otoliths (Prosser and Brown, 1961) occur in the utricle itself, endolymphic currents are then set up in the direction of the stereocilia or the kinocilia, which are accompanied by the appropriate biopotential indicators.

Variations in directional movement of the endolympha must be dependent on changes in the position of the animal in the gravitational field, and especially during radial accelerations. Special electrophysiological studies are necessary in this regard. It is known that excitation of the utricle by changes in the position of the animal's head are accompanied by the appearance of activity currents, which have been studied in neurons of the first type in lower vertebrates (Löwenstein, 1950; Schöne, 1959), and in neurons of the second type in the medulla oblongata of higher vertebrates (Adrian, 1949; Gernand, 1949, 1959; Rupert et al., 1962; O. G. Gazenko et al., 1963).

Thus, comparative study of the cellular and subcellular organization of the utricle makes it possible to make an approach to deciphering the mechanism of its functioning, particularly in regard to the nature of stimulation of the "organ of gravity", which remains constant for all vertebrates. Apparently this must be related both to sudden movements of the otoliths and their transmission to the bundle of stereocilia, and to the directional currents set up simultaneously in the endolympha beneath the otolithic membrane, which are perceived by the individual movable kinocilium.

But what happens during stimulation in the receptor cells of the utricle themselves, particularly during radial accelerations? We have succeeded in establishing that during such stimulation, shifts in the substructural and cytochemical organization of the nucleus and cytoplasm are observed primarily in the ciliated cells. These consist of the displacement of the nucleolus toward the nuclear membrane and the release of its RNA (as ribose) from the nucleus into the cytoplasm, where they immediately induce the formation of a limited segment of endoplasmic (linin) network; under a light microscope, the latter appears to be the nucleolus, which seems to have moved outside the nucleus.

These processes are particularly demonstrable in the guinea pig (Figure 2), and also in monkeys and birds. In guinea pigs the release of the RNA from the nucleolus in the direction of the vector of the gravitational field, i.e., toward the basal pole, where they cause the

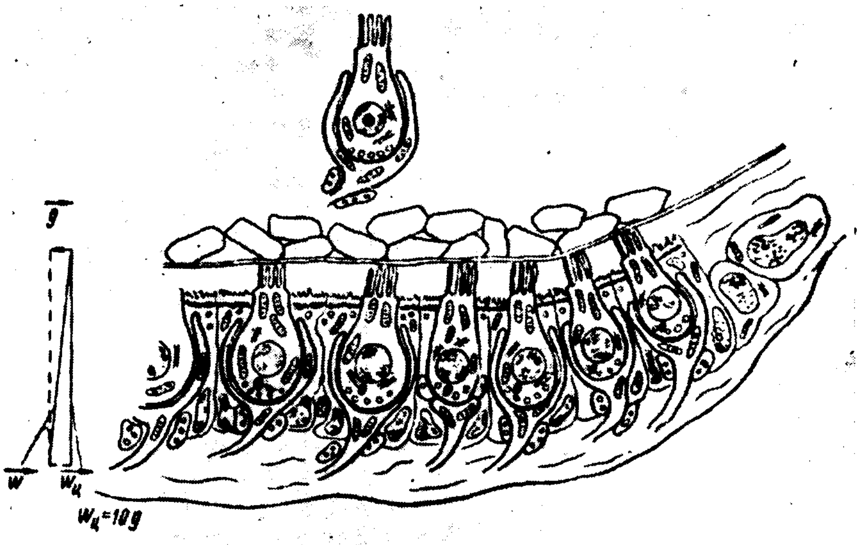

Figure 2. Utricle of a guinea pig subjected to a centrifugal acceleration of 10 G for 3 min. Hair cells are shown in longitudinal cross section through the utricle. Above the cilia, on the otolithic membrane, are the otoliths. The nucleolic RNA expelled from the nuclei of the hair cells into the basal part of the cytoplasm are oriented in the direction of the vector of the gravitational field. A hair cell is shown above of an animal in a state of comparative rest. The RNA of the nucleolus and ctyoplasm is shown in black. At left is a pointer showing the direction of the gravitational field vector.

formation of a segment of endoplasmic network, is most clearly visible following exposure to an acceleration of 10 G for 3 min in type 1 recptor cells (Figure 3). Apparently, in these animals such a directional release of nucleolic RNA into the cytoplasm may also occur spontaneously, without experimental intervention, reflecting some sort of temporally rhythmic release of RNA from the nucleus into the cytoplasm.

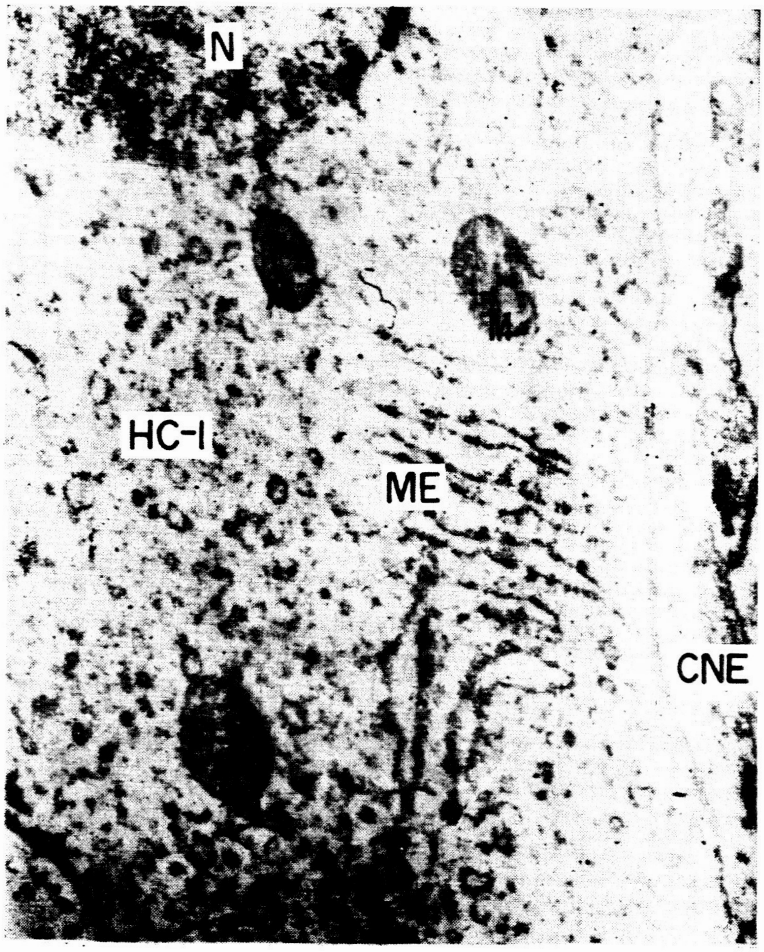

Figure 3. Section through the basal part of a type 1 hair cell from the utricle of a guinea pig following a single exposure of the animal to a radial acceleration of 10 G for 3 min. Formation of the membranes of the endoplasmic network. Electron microphotograph enlarged 26,000 times.

HC-1—type 1 hair cell; N—nucleus; ME—membranes of the endoplasmic network; CNE—cup-shaped nerve ending; M—mitochondria.

In our opinion, this displacement of RNA from the nucleolus through the nuclear membrane into the cytoplasm, where it primarily brings about a local protein synthesis, is possibly the result of the mechanical action of the gravitational field. Gradually, in the course of evolution, this phenomenon became an adaptational factor aiding in protein regeneration compensating the considerable expenditures of structural and functional proteins (enzymes) made by excited receptor cells in the course of their intensive functioning during exposure to accelerations.

In monkeys and birds, which are evidently distinguished by great sensitivity to accelerations, and in whose utricular hair cells the endoplasmic network with riboses may be found both in the basal and in the apical parts of the receptor cell, release of nucleolic RNA can take place in either the one or the other direction.

Of course the phenomenon observed by us (Ya. A. Vinnikov et al., 1963), of the displacement of nucleolic RNA from the nucleus into the cytoplasm, while it clearly illustrates the protein-synthetic function of the nucleic acids even when experimentally caused by acceleration changes in the force of gravity, has a general biological significance as well. It demonstrates a spatial regularity related to the release of RNA from the nucleus into the cytoplasm, where it induces the formation of endoplasmic membranes currently thought to participate in the protein synthesis of all cells (Polikar and Bo, 1962).

Displacement of the nucleolus from the nucleus into the cytoplasm has been observed several times under the light microscope (Kedrovskiy, 1959; Bennet, 1961; Tewari and Bourne, 1962; and others). This phenomenon was regarded as a picture of transfer into the cytoplasm of large packets of RNA, and recently of a number of enzymes as well. Pictures obtained with the electron microscope in our case show the manner in which the granules of nucleolic RNA, after leaving the nucleus and forming a number of endoplasmic network membranes around themselves in the cytoplasm as a result of their spatial displacement through and simultaneous transformation of the cytoplasm, apparently enter upon their function of synthesis.

The described phenomenon was studied by both qualitative and quantitative cytophotometric methods. The composition of the nucleic acids and proteins, including the functional groups of protein molecules (the SS, SH, and COOH groups), were studied at various stages of restoration following single exposures to radial back-chest accelerations of 10 G for 3 min, and at various time periods following repeated exposures.

According to our data, the above-mentioned exposure causes exhaustion of the basal reserve of cytoplasmic granular RNA and the release into its place of nucleolic RNA from the nucleus. The RNA granules released from the nucleus accumulate at first as rods oriented along the vector of the acceleration force; these accumulations take on a circular, and then a triangular form. They gradually increase in size, dilate, and move further to the base of the cell. In this manner, the basal reserve of cytoplasmic granular RNA is restored. This is indicated by the appearance of the characteristic "caplets", which under the electron microscope have the appearance of a spiral endoplasmic network sown with ribosomes. This process, which begins immediately following experimental exposure, continues thereafter in cycles which gradually increase with time. But in guinea pigs, as mentioned above, a secondary spontaneous release of RNA from the nucleolus may be observed in the receptor cells of the utricle after the first experimental rotation (as a rule, 4 days afterwards).

The release into the cytoplasm of nucleolic RNA, which may include coded RNA in its makeup, apparently represents a rhythmic process related to general protein synthesis, which may be disrupted by experimental exposure to acceleration and become asynchronous in the individual receptor cells of the utricle.

Photometric analysis has shown that following the restoration of RNA, there begins a process of increased protein synthesis, which, reaching a certain maximum point, drops again almost to normal and then rises again, forming a curve with several peaks, the highest of which occurs 2 days after a single experimental exposure (Figure 4). Repeated experimental exposures at the maximum points of protein synthesis (1 hour, and 2, 8, and 12 days) apparently have an unfavorable effect, causing impairment or even cessation of protein synthesis.

The greatest reinforcing effect on protein synthesis is shown by repeated experimental exposures administered at those times when RNA restoration has occurred but protein synthesis has not yet begun (namely, 8 hours, and 3 and 6 days after a single exposure). However, experimental reexposure after 5 days causes a sharp drop in protein synthesis, followed by formation of vacuoles in the cytoplasm and nucleus, edema of the cup-shaped nerve endings, pycnosis of the nucleus, etc. Thus, these stages (5th day) may be regarded as "critical", inasmuch as they are the most vulnerable times for repeated experimental exposures.

So it is that in the receptor cells of the utricle in guinea pigs, monkeys, and doves stimulated by exposure to radial acceleration, a regular cycle of cytochemical shifts related to the protein synthesis function of the nucleic acids (RNA) is observed. These shifts may apparently be regarded as reflecting the synthetic function of the receptor cells of the "organ of gravity" during stimulation.

Change in the protein regime of the receptor cells coincides with changes (i.e., increase at the onset and decrease in the final periods

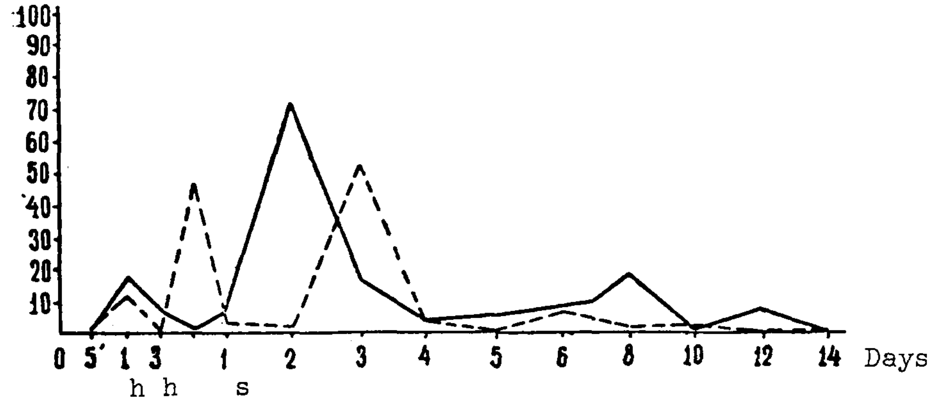

Figure 4. Curve showing changes in the arithmetic mean (M) of variational curves of the optical density of proteins in the basal parts of receptor cells (from cytophotometric data) at various stages of restoration following single exposures to centrifuging (solid line) and repeated centrifugings (broken line). The horizontal axis represents time elapsed after centrifuging. The vertical axis gives arbitrary units of optical density in millimeters of the microphotometer scale (model MF-4).

of experimental exposure) in the activity of reducing enzymes in the mitochondria (Figure 5) and acetylcholinesterase (Figure 6) in the synapses of the hair cells of the utricle, as observed by us and our colleagues (Ya. A. Vinnikov and L. K. Titova, 1962; Ya. A. Vinnikov, O. G. Gazenko, L. K. Titova, and A. A. Bronshteyn, 1963; L. K. Titova and Ya. A. Vinnikov, 1964). At the present time it has been possible to make these cytochemical data more precise in many respects by means of the electron microscope. Thus, in the area of the cup-shaped sinapses of type 1 cells, rod-shaped thickenings were discovered in the presynaptic membrane, which are apparently related to the localization of acetylcholinesterase. These thickenings of the synaptic membrane are strewn with numerous synaptic vesicles, which are currently thought to be filled with acetylcholine (Whittaker and Gray, 1962; Robertis et al., 1962).

In experimental acceleration, the picture of penetration of synaptic vesicles into the intersynaptic space is observed. No less indicative are the pictures of the distribution of mitochondria in the vicinity of the synapses. These carriers of reducing enzymes and ATP in the body of the cell may flatten and spread out against the presynaptic membrane. In the cup-shaped nerve endings they are distinguished by their large, circular outlines and the characteristic equatorial location of their crista.

Figure 5. Localization of succinate, dehydrogenase in the mitochondria of branching nerve fibers and cup-shaped endings encasing the jug-shaped hair cells of the acoustic spot of a land turtle:

a--animal in a state of comparative rest;

b--after centrifuge acceleration (18 doses of 20 revolutions) at a speed of 40 rpm, with pauses of 10 seconds between doses. Histological section. Approximately 10 x 60 rpm.

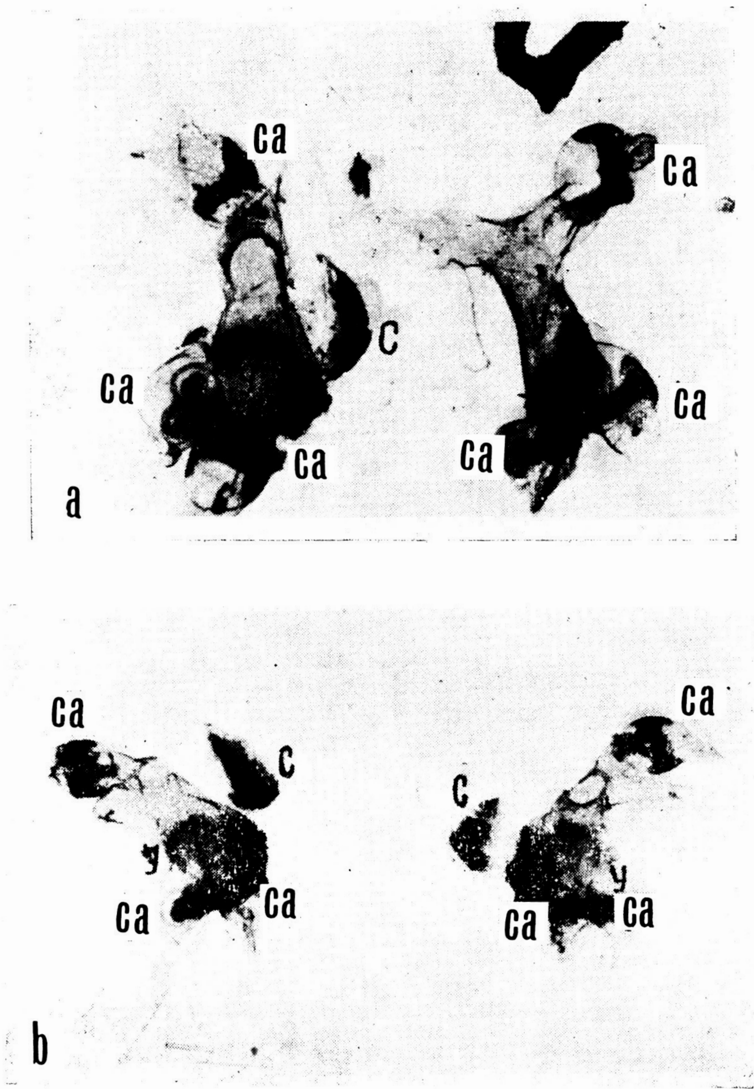

Figure 6. Localization of acetylocholinesterase in the vicinity of the receptor structures of the vestibule of the labyrinth of a cat:

a—control animal; b—after acceleration, 10 G for 3 min. Integral specimen. Illuminated enlargement. ca—cristae ampullaris; Y—utricle; C—sacculus.

In the cup-shaped nerve endings, the mitochondria occur in the form of alternating moniliform bodies which take up practically the whole of the neuroplasm. Thus, the disposition of the mitochondria in the vicinity of the synapse demonstrates still once more the specific energetic role of nonspecific energy metabolism in the transmission of nerve impulses (Ya. A. Vinnikov and L. K. Titova, 1962).

In summarizing the above, it can be concluded that the shifts observed in the substructural and cytochemical organization of the ciliated cells and synapses of the utricle during acceleration apparently reflect a state of excitation and transmission of impulses. This state is characterized by a series of biochemical processes distinguished by strict substructural organization. These processes are directly related to the function of the nucleic acids, i.e., to protein synthesis. The results obtained reveal to some extent the mechanism of the functioning of the "organ of gravity" on the cellular and subcellular levels of organization and indicate methods and possibilities of controlling its functioning under conditions of acceleration and space flight. However, the processes of specific stimulation of the "organ of gravity" (the utricle), as well as the interdependence of its activity with that of other receptor elements of the vestibular system in vertebrates, remain unclear. Their elucidation is the order of the day.

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